REMARKS

Claims 1 to 38 are pending, with claims 2 to 7, 11 to 14 and 16 to 25 withdrawn from consideration as allegedly drawn to non-elected inventions. Claim 1, as well as non-elected claims 2 to 7, 11 to 14 and 16 to 25, have been canceled herein. Thus, claims 8 to 10, 15, and 26 to 38 are pending and presently under examination.

Regarding the Rejections

Regarding the enablement rejection under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1, 8 to 10, 15 and 26 to 38 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement, are respectfully traversed. Although the Office Action acknowledges that the specification enables the use of three specific VEGFR-3 kinase inhibitors (MAE87, MAE106 and MAZ51), it is alleged that the specification does not teach how to make or use other VEGFR-3 inhibitors including kinase inhibitors. In particular, the Office Action asserts that one skilled in the art is not taught how to make the recited VEGFR-3 kinase inhibitors because there is insufficient guidance as to their structures without the disclosure of amino acid sequences or chemical structures. The Office Action also asserts that there are insufficient *in vivo* working examples demonstrating that all VEGFR-3 inhibitors are effective for extending corneal graft survival and that the specification neglects to disclose which conformational changes and amino acid contacts between an inhibitor and the VEGFR-3 receptor are responsible for inhibiting lymphangiogenesis. Given that the elected subject matter is directed to methods practiced with a VEGFR-3 kinase inhibitor, Applicant responds to the rejection as it pertains to this subject matter.

Applicant submits that the specification provides sufficient guidance regarding how to make and use the invention with a variety of VEGFR-3 kinase inhibitors including, but not limited to, MAE87, MAE 106 and MAZ51. First, the specification provides general characteristics of VEGFR-3 kinase inhibitors, teaching that such inhibitors can be, for example, ATP analogs, or other molecules that bind the VEGFR-3 catalytic domain (page 21, lines 1-3). As set forth in the specification, a VEGFR-3 kinase inhibitor can, for example, bind the VEGFR-3 catalytic domain through one or more hydrogen bonds similar to those anchoring the adenine moiety of ATP to the receptor or can bind the hydrophobic pocket adjacent to the adenine

binding site (page 21, lines 4-13). As further guidance to the skilled person, the specification discloses several species of VEGFR-3 kinase inhibitor, namely the MAE87, MAE 106 and MAZ51 inhibitors described in Kirkin et al., Eur. J. Biochem. 268:5530-5540 (2001), providing both the structures of these inhibitors (page 56) as well as exemplary methods for their preparation (page 21, lines 14-21). Thus, as guidance to the skilled person, the specification provides both general characteristics as well as specific examples of VEGFR-3 kinase inhibitors. In view of this guidance, one skilled in the art would have been able to practice the full scope of the invention without undue experimentation.

As additional guidance to the skilled person regarding how to make and use the claimed invention, the specification teaches that one skilled in the art can identify additional VEGFR-3 kinase inhibitors using routine techniques. In this regard, the specification teaches a well-known assay for identifying VEGFR-3 kinase inhibitors by detecting production of phosphorylated tyrosine with anti-phosphotyrosine antibody. As guidance to the skilled person, an exemplary protocol for detection of phosphorylated tyrosine by ELISA is set forth in the specification at page 22, lines 1-24; such assays are routine and well known in the art, as described, for example, in Hennequin et al., J. Med. Chem. 42:5369-5389 (1999), and Wedge et al., Cancer Res. 60:970-975 (2000), which are incorporated into the specification (page 21, line 27, to page 22, line 1; and page 57, lines 14-17). Briefly, one skilled in the art can incubate a potential inhibitor with the VEGFR-3 cytoplasmic receptor domain in an appropriate buffer in the presence of ATP, with subsequent detection of phosphorylated tyrosine using a commercially available anti-phosphotyrosine antibody (page 22, lines 6-19). A reduction in the amount of phosphorylated tyrosine in the presence of the proposed kinase inhibitor, as compared to the amount of phosphorylated tyrosine in the absence of the proposed inhibitor, indicates kinase inhibitory activity. Thus, using the guidance in the specification, one skilled in the art would have been able to use well-known methods to screen for, or corroborate the activity of, VEGFR-3 kinase inhibitors. The use of such routine methods does not constitute undue experimentation.

The Office Action further asserts that, given the indefinite number of undisclosed VEGFR-3 inhibitors, there is insufficient guidance as to which conformational changes and amino acid contacts with VEGFR-3 are responsible for inhibiting lymphangiogenesis. In response, Applicant respectfully points out that it is not necessary to describe a mechanism of action in order to teach how to make and use the invention. As set forth above, kinase inhibitory activity can be identified or corroborated without knowledge of the inhibitor-receptor contacts.

Furthermore, in the opinion of the Examiner, there are insufficient *in vivo* working examples demonstrating that all VEGFR-3 inhibitors are effective for extending corneal graft survival, asserting that, even if an inhibitor binds to VEGFR-3, binding will not necessarily inhibit lymphangiogenesis. Firstly, Applicant need not demonstrate that all VEGFR-3 kinase inhibitors would function to extend corneal graft survival in the methods of the invention. Rather, it is well-established that claims are permitted to encompass inactive embodiments. Thus, even if, for the sake of argument, some VEGFR-3 kinase inhibitors do not inhibit lymphangiogenesis, enablement of the claims would not be precluded. Secondly, Applicant would respectfully point out that the Examiner has not provided any evidence or reasoning as required under MPEP 2164.04 as to why one skilled in the art would expect some, but not all, VEGFR-3 kinase inhibitors to inhibit lymphangiogenesis and, thus, to extend corneal graft survival. Without evidence or specific reasoning to the contrary, one skilled in the art would have understood that the highly conserved tyrosine kinase domain of VEGFR-3 (see page 12, lines 14-17) was critical to activity of the receptor and would have expected that a variety of VEGFR-3 kinase inhibitors would disrupt the activity of VEGFR-3, including its lymphangiogenic activity, as taught in the subject application. Given that the Examiner has not established a *prima facie* case of lack of enablement, Applicant further respectfully requests that this ground for rejection be removed.

Having addressed each of the grounds for rejection of the claims as allegedly lacking enablement under 35 U.S.C. § 112, first paragraph, Applicant respectfully requests that the Examiner reconsider and remove the enablement rejection of claims 1, 8 to 10, 15 and 26 to 38.

Regarding the written description rejection under 35 U.S.C. § 112, first paragraph

The objection to the specification and corresponding rejection of claims 1, 8 to 10, 15 and 26 to 38 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description, is respectfully traversed. The Office Action alleges that the claimed methods include subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. In particular, the Office Action alleges that the specification does not reasonably provide written description of any "vascular endothelial growth factor receptor-3

(VEGFR-3) inhibitor," any "anti-angiogenic agent" and any "immunosuppressive agent." Applicant respectfully disagrees with the rejection. Given that the elected claims recite the use of a VEGFR-3 "kinase inhibitor," Applicant will address this rejection as it pertains to VEGFR-3 kinase inhibitors, anti-angiogenic agents and immunosuppressive agents.

Regarding written description for "VEGFR-3 kinase inhibitors"

Applicant submits that the specification describes the genus of VEGFR-3 kinase inhibitors in such a way as to reasonable convey to one skilled in the relevant art that the inventor had possession of the claimed invention at the time the application was filed. In this regard, the specification describes a VEGFR-3 inhibitor as an inhibitor of receptor tyrosine kinase activity that selectively or non-selectively reduces tyrosine kinase activity of a VEGFR-3 receptor (page 20, lines 24-28). The specification further describes structural and functional characteristics of the recited genus of VEGFR-3 kinase inhibitors. As set forth in the specification, a VEGFR-3 kinase inhibitor useful in the invention can have the structure, for example, of an ATP analog, or can have the function of binding the VEGFR-3 catalytic domain (page 21, lines 1-13). Members of the genus of VEGFR-3 kinase inhibitors are further functionally characterized in the specification by the ability to reduce production of phosphorylated tyrosine as determined by ELISA assay using a mouse IgG anti-phosphotyrosine antibody (page 21, line 27, to page 22, line 24). Additional written description is provided by the disclosure of MAE87, MAE 106 and MAZ51 and their structures as exemplary species of VEGFR-3 kinase inhibitor (page 21, lines 14-21; page 56). In sum, in addition to describing exemplary species, the specification describes structural and functional characteristics of the recited genus of VEGFR-3 kinase inhibitors which are sufficient to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. Accordingly, Applicant respectfully requests that the Examiner remove this ground for rejecting claims 1, 8 to 10, 15 and 26 to 38 as allegedly lacking written description.

Regarding written description for "anti-angiogenic agents"

The specification also provides sufficient written description for the genus of anti-angiogenic agents. As set forth at page 41, lines 3-10, the specification describes an anti-angiogenic agent as a molecule that reduces or inhibits angiogenesis, which is the formation of

new blood vessels. In the methods of the invention, an anti-angiogenic agent is optionally administered in conjunction with a VEGFR-3 inhibitor (page 40, line 24, to page 41, line 2). The specification further provides written description for the genus of anti-angiogenic agents by disclosing a variety of exemplary species including, for example, angiostatin, endostatin, metastatin, and 2ME2; anti-VEGF antibodies such as Avastin; and VEGFR-2 inhibitors such as SU5416 and SU6618 (page 43, lines 9-23). Several of these molecules are commercially available from sources such as EntreMed (Rockville, MD), Genentech (South San Francisco, CA) and SUGEN (South San Francisco, CA), as disclosed at page 43, lines 9-18. As described in the specification, additional species of anti-angiogenic agents useful in the invention include, for example, inhibitors of VEGF; inhibitors of fibroblast growth factors such as FGF-1, FGF-2, FGF-4 or FGF-5; heparin-binding fragments of fibronectin; modified forms of antithrombin; collagenase inhibitors; angiostatic steroids; platelet factor 4; thrombospondin; and doxorubicin (page 42, line 1, to page 43, line 8). In sum, in view of the description of a variety of exemplary species as well as functional characterization of the genus of anti-angiogenic agents, one skilled in the art would have appreciated that the inventor had possession of the claimed invention at the time the application was filed.

Regarding written description for "immunosuppressive agents"

Applicant submits that the specification provides written description sufficient to convey to one skilled in the relevant art that the inventor had possession of the genus of "immunosuppressive agents." In this regard, the specification discloses a variety of exemplary immunosuppressive agents including corticosteroids and other steroids such as prednisolone acetate, cyclosporin and tacrolimus (FK506), and therapeutic monoclonal antibodies including anti-T lymphocyte, anti-CD4+ cell, anti-ICAM-1 and anti-IL-2 antibodies (page 44, line 1, to page 45, line 4). Thus, in view of the description in the specification, one skilled in the relevant art would have appreciated that the invention had possession of the invention at the time the application was filed. Accordingly, Applicant respectfully requests that the Examiner reconsider and remove this ground for rejection.

Having addressed each of the several grounds for rejection above, Applicant respectfully requests that the Examiner reconsider and remove the rejection of claims 1, 8 to 10, 15 and 26 to 38 under 35 U.S.C. § 112, first paragraph, as allegedly lacking written description.

Regarding the rejection of claims 1 and 29 under 35 U.S.C. § 103

The rejection of claims 1 and 29 under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al. and Veikkola et al. is respectfully traversed. The cited publication by Herbort et al. allegedly reports improving corneal graft survival by administering to a rat cyclosporine A (CsA), an immunosuppressive agent that reduces graft neovacularization. While Herbort et al. reports the use of cyclosporine A, this reference does not teach or suggest a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor or its use in extending corneal graft survival. Mimura et al. report that lymphatic vessels may contribute to decreased success of keratinoplasty by accelerating antigen recognition and graft rejection and that VEGFR-3 and its ligand, VEGF-C, play a role in corneal lymphangiogenesis. Veikkola et al. report that growth of new blood and lymphatic vessels requires activation of VEGFR-3, and that VEGFR-3 inhibitors such as soluble VEGFR-3 can block hyperplastic growth of lymphatic vessels. The Office Action concludes that one skilled in the art would have had a reasonable expectation of success in extending corneal graft survival by substituting the VEGFR-3 inhibitors of Veikkola et al. for the cyclosporin A used by Herbort et al.

Applicant submits that the methods of the invention would not have been obvious over the cited references by Herbort et al., Mimura et al. and Veikkola et al. The claimed methods involve administering to a patient an effective amount of a pharmaceutical composition including a vascular endothelial growth factor receptor-3 (VEGFR-3) inhibitor, whereby lymphangiogenesis is suppressed in the cornea of the patient. The cited references, neither alone nor in combination, provide one skilled in the art with a reasonable expectation of success in extending corneal graft survival by using a VEGFR-3 inhibitor to suppress lymphangiogenesis. Specifically, the primary reference by Herbort et al. reports that systemic cyclosporine A prevented corneal graft rejection and additionally *was associated with* reduced graft neovascularization. Herbort et al. do not demonstrate that the observed reduction in graft neovascularization was responsible for the enhanced corneal graft survival. See, for example, page 219, first full paragraph, which indicates that cyclosporine (CsA) prevent graft rejection during the time of its administration and also significantly reduced vessels in the graft but does not indicate that the reduction in vasculaturization was causative of delayed graft rejection. Thus, at best, the results of Herbort et al. are consistent with a mere correlation between

neovascularization and graft rejection but do not show that inhibition of new blood vessel formation is sufficient to prevent graft rejection.

Furthermore, the cited references, neither alone nor in combination, teach or suggest extending corneal graft survival by substitution of a VEGFR-3 inhibitor for cyclosporin in the methods of Herbort et al. The cited reference by Mimura et al. at best reports that formation of lymphatic vessels *may* contribute to graft rejection. See, for example, page 71, first column, which indicates that "lymphatic vessels *may* contribute to a decreased success rate of keratoplasty in vascularized cornea" and that "inhibition of lymphatic vessels...*may* improve the outcome of keratoplasty" (emphasis added). Thus, at best, Mimura et al. provide one skilled in the art with a motivation to try the claimed methods. However, the cited publication by Mimura et al., neither alone nor in combination with the other cited references, provides one skilled in the art with a reasonable expectation of success in using VEGFR-3 inhibitors to extend corneal graft survival. Similarly, the cited publication by Veikkola et al., although it reports that soluble VEGFR-3 can reduce hyperplastic growth of lymphatic vessels, does not teach or suggest that a VEGFR-3 inhibitor can extend corneal graft survival. In sum, the cited references collectively provide, at best, a tentative suggestion *to try*; however, the cited references, neither alone nor in combination, provide one with a reasonable expectation of success in extending corneal graft survival using a VEGFR-3 inhibitor to suppress lymphangiogenesis.

Additionally, Cohen et al., Curr. Eye Res. 13:139-144 (1994), attached as Exhibit A, teaches away from the claimed methods of using vascular inhibitors for extending corneal graft survival. Specifically, in their 1994 publication, Cohen et al. inhibit allograft vascularization in an attempt to improve corneal graft survival. The authors found that the platelet-activating factor (PAF) antagonist, BN52021, inhibited corneal graft vascularization for up to 10 days after transplantation (see page 139, abstract; and page 142, Figure 3). However, there was no significant difference in corneal graft survival time between PAF antagonist (BN52021)-treated and control corneas. See, for example, Table 2 and the final paragraph at page 141, which states: "Grafts in saline-treated eyes and BN52021-treated eyes exhibited similar mean survival times." Thus, Cohen et al. were not successful in extending corneal graft survival by inhibiting allograft vascularization and, therefore, teach away from the claimed invention.

In view of the above remarks, Applicant respectfully requests that the Examiner remove the rejection of claims 1 and 29 under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al. and Veikkola et al.

Regarding the rejection of claims 8 to 10 under 35 U.S.C. § 103

Claims 8 to 10 are drawn to methods of extending corneal graft survival using a VEGFR-3 kinase inhibitor, a VEGFR-3 kinase inhibitor which binds the VEGFR-3 catalytic domain or a VEGFR-3 inhibitor which is an ATP analog. The rejection of these claims under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al. and Veikkola et al. as applied to claims 1 to 29 above, and further in view of Kirkin et al., is respectfully traversed.

The cited references by Herbort et al., Mimura et al. and Veikkola et al. have been discussed above. The cited reference by Kirkin et al. reports VEGFR-3 kinase inhibitors which are ATP analogs and which bind to the VEGFR-3 catalytic domain and further reports that these inhibitors can be useful for inhibiting VEGFR-3-mediated lymphangiogenesis.

Applicant submits that claims 8 to 10 are unobvious over the cited references for the reasons discussed above in regard to claims 1 and 29. Specifically, neither Herbort et al., Mimura et al. nor Veikkola et al., either alone or in combination, provide one skilled in the art with a reasonable expectation of success in extending corneal graft survival by using a VEGFR-3 inhibitor to suppress lymphangiogenesis. Herbort et al. report that treatment with the immunosuppressive agent cyclosporin both reduces graft vascularization and improves graft survival, but does not teach or suggest the use of VEGFR-3 inhibitors for extending corneal graft survival. Mimura et al. suggest that lymphatic vessels may possibly contribute to a decreased success of keratinoplasty but do not provide one skilled in the art with a reasonable expectation of success in extending corneal graft survival by administering an effective amount of a pharmaceutical composition containing a VEGFR-3 inhibitor. The cited publication by Veikkola et al. relates to the use of VEGFR-3 inhibitors such as soluble VEGFR-3 for reducing the growth of lymphatic vessels but does not teach or suggest the use of VEGFR-3 inhibitors for extending corneal graft survival. Similarly, the cited publication by Kirkin et al. reports VEGFR-3 inhibitors, which in this case are small molecule inhibitors of VEGFR-3 kinase activity, but does not teach or suggest the use of VEGFR-3 inhibitors for extending corneal graft survival. Thus,

Kirkin et al. does not supply what is lacking in the earlier cited references. Accordingly, claims 8 to 10 are unobvious over Herbort et al. in view of Mimura et al., Veikkola et al., and Kirkin et al.

In view of the above remarks, Applicant respectfully requests that the Examiner remove the rejection of claims 8 to 10 under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al., Veikkola et al. and Kirkin et al.

Regarding the rejection of claims 8 to 10 under 35 U.S.C. § 103

The rejection of claims 26 to 28 and 30 to 38 under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al. and Veikkola et al. as applied to claims 1 to 29 above, and further in view of Yamagami et al., Hikita et al. and U.S. Patent No. 6,331,313 is respectfully traversed.

Claims 26 to 28 and 30 to 38 are directed to methods of extending corneal graft survival by administering a VEGFR-3 kinase inhibitor in addition to another agent such as an anti-angiogenic agent or immunosuppressive agent; administering the VEGFR-3 kinase inhibitor repeatedly or at specific times; or administering the VEGFR-3 kinase inhibitor using a specific route of administration.

Claims 26 to 28 and 30 to 38 are unobvious over Herbort et al. in view of Mimura et al., Veikkola et al.,Yamagami et al., Hikita et al. and U.S. Patent No. 6,331,313, essentially for the reasons discussed above in regard to the rejection of claims 1 and 29. As discussed above, neither Herbort et al., Mimura et al., or Veikkola et al., alone or in combination, provide one skilled in the art with a reasonable expectation of success in extending corneal graft survival using a VEGFR-3 kinase inhibitor. Neither do Yamagami et al., Hikita et al. or U.S. Patent No. 6,331,313 provide what is missing in the primary references. At best, Yamagami et al. report treatment of corneal grafts using combination therapy including administration of an immunosuppressive agent but do not teach or suggest that a VEGFR-3 kinase inhibitor can extend corneal graft survival. Hikita et al. report that local and topical administration of immunosuppressive agents can avoid systemic effects when treating patients following corneal graft transplantation. However, Hikita et al. do not teach or suggest the use of VEGFR-3 kinase inhibitors for extending corneal graft survival. U.S. Patent No. 6,331,313 reports the use of intraocular and periocular implants for local drug release but, again, does not teach or suggest the

use of VEGFR-3 inhibitors for extending corneal graft survival. In sum, the cited references by Yamagami et al., Hikita et al. or U.S. Patent No. 6,331,313, neither alone nor in combination with Herbort et al., Mimura et al., and Veikkola et al. provide one with a reasonable expectation of success in extending corneal graft survival using a VEGFR-3 kinase inhibitor to suppress lymphangiogenesis.

For the foregoing reasons, Applicant submits that claims 26 to 28 and 30 to 38 are unobvious over the cited references and respectfully requests that the Examiner remove the rejection of claims 26 to 28 and 30 to 38 under 35 U.S.C. § 103 as allegedly obvious over Herbort et al. in view of Mimura et al. and Veikkola et al., and further in view of Yamagami et al., Hikita et al. and U.S. Patent No. 6,331,313.

CONCLUSION

In view of the above remarks, Applicant submits that the claims are now in condition for allowance and respectfully requests a notice to that effect. Should the Examiner have any questions, he is invited to contact the undersigned agent or Cathryn Campbell.

Respectfully submitted,

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